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(FILE 'HOME' ENTERED AT 19:24:01 ON 19 MAR 2003)

FILE 'REGISTRY' ENTERED AT 19:24:20 ON 19 MAR 2003
E "EXANOPARIN"/CN 25
E "ENOXAPARIN"/CN 25
L1 2 S E3 OR E4

FILE 'CAPLUS' ENTERED AT 19:25:08 ON 19 MAR 2003
L2 21296 S L1
L3 1469 L2 AND (METALLOPROTEIN? OR COLLAGEN? OR NEUTROPHIL? OR AGGRECAN
L4 742 L2 AND (METALLOPROTEIN? OR COLLAGENASE? OR NEUTROPHIL? OR AGGRE
L5 402 L2 AND (METALLOPROTEIN? OR COLLAGENASE? OR NEUTROPHIL? OR AGGRE
L6 162 L2 AND (METALLOPROTEINASE? OR COLLAGENASE? OR AGGRECANASE? OR H
L7 138 L6 NOT PY>2001
L8 127 L6 NOT PY>2000
L9 45 L2 (2S) (METALLOPROTEINASE? OR COLLAGENASE? OR AGGRECANASE? OR

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L9 ANSWER 1 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:541384 CAPLUS
DOCUMENT NUMBER: 138:22953
TITLE: Von Willebrand factor-cleaving protease (ADAMTS13) in thrombocytopenic disorders: a severely deficient activity is specific for thrombotic thrombocytopenic purpura
AUTHOR(S): Bianchi, Valentina; Robles, Rodolfo; Alberio, Lorenzo; Furlan, Miha; Lammle, Bernhard
CORPORATE SOURCE: Central Hematology Laboratory, University Hospital, Inselspital, Bern, CH-3010, Switz.
SOURCE: Blood (2002), 100(2), 710-713
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A severe deficiency in von Willebrand factor-cleaving protease (ADAMTS13) activity (< 5% that in normal plasma) has been observed in most patients with a diagnosis of thrombotic thrombocytopenic purpura (TTP) but not in those with a diagnosis of hemolytic uremic syndrome. However, ADAMTS13 deficiency has been claimed not to be specific for TTP, since it was observed in various thrombocytopenic and other conditions. We studied 68 patients with thrombocytopenia due to severe sepsis or septic shock (n = 17), heparin-induced thrombocytopenia (n = 16), idiopathic thrombocytopenic purpura (n = 10), or other hematol. (n = 15) or miscellaneous conditions (n = 10).
Twelve of the 68 patients had subnormal levels of ADAMTS13 activity (≤ 30%), but none had less than 10%. Thus, the study showed that ADAMTS13 activity is decreased in a substantial proportion of patients with thrombocytopenia of various causes. A severe deficiency of ADAMTS13 (< 5%), identified in more than 120 patients during 1996 to 2001 in our laboratory, is specific for a thrombotic microangiopathy commonly labeled TTP.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 45 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:445207 CAPLUS
DOCUMENT NUMBER: 138:1588
TITLE: ADAMTS1 cleaves aggrecan at multiple sites and is differentially inhibited by metalloproteinase inhibitors
AUTHOR(S): Rodriguez-Manzaneque, Juan Carlos; Westling, Jennifer; Thai, Shelley N.-M.; Luque, Alfonso; Knauper, Vera; Murphy, Gillian; Sandy, John D.; Iruela-Arispe, M. Luisa
CORPORATE SOURCE: Department of Molecular, Cell and Developmental Biology, Molecular Biology Institute, University of California at Los Angeles, Los Angeles, CA, 90095, USA
SOURCE: Biochemical and Biophysical Research Communications (2002), 293(1), 501-508
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ADAMTS1 is a secreted protein that belongs to the recently described ADAMTS (a disintegrin and metalloprotease with thrombospondin repeats) family of proteases. Evaluation of ADAMTS1 catalytic activity on a panel of extracellular matrix proteins showed a restrictive substrate specificity which includes some proteoglycans. Our results demonstrated that human ADAMTS1 cleaves aggrecan at a previously shown site by its mouse homolog, but we have also identified addnl. cleavage sites that ultimately confirm the classification of this protease as an "aggrecanase". Specificity of ADAMTS1 activity was further verified when a point mutation in the zinc-binding domain abolished its catalytic effects, and latency conferred by the prodomain was also demonstrated using a furin cleavage site mutant. Suppression of ADAMTS1 activity was accomplished with a specific monoclonal antibody and some metalloprotease inhibitors, including tissue inhibitor of metalloproteinases 2 and 3. Finally, we developed an activity assay using an artificial peptide substrate based on the interglobular domain cleavage site (E373-A) of rat aggrecan.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:926012 CAPLUS
DOCUMENT NUMBER: 136:161674
TITLE: Angiotensin II signaling and HB-EGF shedding via metalloproteinase in glomerular mesangial cells
AUTHOR(S): Uchiyama-Tanaka, Yoko; Matsubara, Hiroaki; Nozawa, Yoshihisa; Murasawa, Satoshi; Mori, Yasukiyo; Kosaki, Atsushi; Maruyama, Katsuya; Masaki, Hiroya; Shibasaki, Yasunobu; Fujiyama, Soichiro; Nose, Atsuko; Iba, Osamu; Hasagawa, Takamasa; Tateishi, Eriko; Higashiyama, Shigeki; Iwasaka, Toshiji
CORPORATE SOURCE: Department of Medicine II, Kansai Medical University, Osaka, Japan
SOURCE: Kidney International (2001), 60(6), 2153-2163
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Angiotensin II (Ang II) has been implicated in the development of

glomerulosclerosis by stimulating fibronectin (FN) synthesis. The processing and release of heparin binding-endothelin growth factor (HB-EGF) are activated by protein kinase C (PKC) and Ca2+ signaling. The authors studied the roles of HB-EGF and endothelial growth factor (EGF) receptor (EGFR) in Ang II-induced FN expression using mesangial cells. Mesangial cells were prepared from mouse kidneys by the explant method and cells were used at passages 4 and 5. Ang II stimulated FN mRNA levels dose-dependently with a maximal increase (3.4-fold) after 12 h of incubation. This action was completely inhibited by PKC inhibitors and slightly blocked by Ca2+ chelating agents. FN mRNA accumulation by Ang II was abolished by tyrosine kinase inhibitors, a specific inhibitor for EGFR (AG1478) and extracellular signal-regulated kinase (ERK) inactivation. Addition of neutralizing anti-HB-EGF antibody, as well as pretreatment with heparin or the metalloproteinase inhibitor batimastat abolished induction of FN expression by Ang II. In mesangial cells stably transfected with a chimeric construct containing HB-EGF and alkaline phosphatase (ALP) genes, ALP activity in incubation medium was rapidly increased by Ang II (1.7-fold at 0.5 min) and reached a 4.1-fold increase at two minutes. Ang II phosphorylated EGFR (maximal at 2 min) and ERK (maximal at 8 min) in a PKC- and metalloproteinase-dependent manner. Ang II stimulated the expression and release of transforming growth factor-β (TGF-β) via EGFR-mediated signaling, and the released TGF-β also contributed to Ang II-mediated FN expression via EGFR transactivation. Ang II-mediated FN expression was regulated by autocrine effects of HB-EGF and TGF-β, suggesting a novel paradigm for cross-talk between Ang II and growth factor receptor signaling pathways.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 45 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:855412 CAPLUS

DOCUMENT NUMBER: 136:196010

TITLE: Construction, Expression, and Characterization of a Baculovirally Expressed Catalytic Domain of Human Matrix Metalloproteinase-9

AUTHOR(S): Sadatmansoori, Sepideh; MacDougall, John; Khademi, Shahram; Cooke, Laurence S.; Guarino, Linda; Meyer, Edgar F.; Forough, Reza

CORPORATE SOURCE: Department of Biochemistry and Biophysics, Health Science Center, Texas A&M University, College Station, TX, 77843, USA

SOURCE: Protein Expression and Purification (2001), 23(3), 447-452
CODEN: PEXPEJ; ISSN: 1046-5928

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We report DNA construction, baculovirus expression, and partial characterization of a minienzyme form of the human matrix metalloproteinase-9 (MMP-9). The MMP-9 minienzyme gene construct consisting of the pre, pro, and catalytic domains of the MMP-9 was introduced into Sf9 insect cells using a baculovirus expression system. The expression of the recombinant MMP-9 minienzyme was evaporating to be approx. 0.8 mg/L of cell medium. The recombinant protein was purified using a single-step gelatin-Sepharose affinity column and yielded a highly stable and active minienzyme with gelatinolytic activity. Moreover, two

interesting findings related to MMP-9 interactions with heparin and TIMP-1 resulted from our studies. First, the pro and catalytic domains of the human MMP-9 are not sufficient for heparin affinity. Second, in contrast to the prevailing consensus, TIMP-1 blockade of the enzymic activity of MMP-9 does not require prior binding to the C-terminus of its MMP-9 protein substrate. (c) 2001 Academic Press.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 45 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:466608 CAPLUS
DOCUMENT NUMBER: 136:67862
TITLE: Expression and induction of collagenases (MMP-8 and -13) in plasma cells associated with bone-destructive lesions
AUTHOR(S): Wahlgren, Jaana; Maisi, Paivi; Sorsa, Timo; Sutinen, Meeri; Tervahartiala, Taina; Pirila, Emma; Teronen, Olli; Hietanen, Jarkko; Tjaderhane, Leo; Salo, Tuula
CORPORATE SOURCE: Faculty of Medicine and Biomedicum, University of Helsinki, Helsinki, FIN-00014, Finland
SOURCE: Journal of Pathology (2001), 194(2), 217-224
CODEN: JPTLAS; ISSN: 0022-3417
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Matrix metalloproteinases (MMPs) collectively degrade extracellular matrix and basement membrane proteins in chronic inflammation and bone-destructive lesions. This study examined the ability of Ig-producing plasma cells, typically present in sites of chronic inflammation, to express collagenases (MMP-8 and -13) in vivo and in vitro. Phorbol-12-myristate-13-acetate, interleukin-6, and tumor necrosis factor-α and heparin with the tumor promoter or cytokines potently enhanced (up to 9-fold) MMP-8 and -13 expression by the RPMI 8226 myeloma cell line, as evidenced by Western blotting and semi-quant. reverse transcriptase-polymerase chain reaction. Immunohistochem. anal. and in situ hybridization revealed that plasma cells expressed MMP-8 and -13 focally in periapical granulomas, odontogenic cysts, and malignant plasmacytomas. MMP-8 and MMP-13 from plasma cells can participate in bone organic matrix destruction at sites of chronic inflammation and neoplastic growth. Since MMP-13 was more frequently expressed than MMP-8 in plasma cells of strongly recurring keratocysts and malignant plasmacytomas, it is concluded that plasma cell MMP-13 has a particularly important role in benign and malignant bone-destructive lesions.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 45 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:374233 CAPLUS
DOCUMENT NUMBER: 135:148983
TITLE: Heparin-Enhanced Zymographic Detection of Matrilysin and Collagenases
AUTHOR(S): Yu, Wei-hsuan; Woessner, J. Frederick, Jr.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL, 33101, USA
SOURCE: Analytical Biochemistry (2001), 293(1), 38-42
CODEN: ANBCA2; ISSN: 0003-2697

PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Unlike the gelatinases (MMP-2 and -9), matrilysin (MMP-7) and collagenases (MMP-1 and -13) are difficult to detect at low levels in conventional casein or gelatin zymog. In this report, heparin was used to enhance the zymog. assays for MMP-7, -1, and -13. With the addition of heparin to the enzyme sample, MMP-7 can be detected at a level of 30 pg in transferrin zymog. and MMP-1 and -13 can be detected at a level of 0.2 ng in gelatin zymog. Carboxymethylated transferrin is used instead of casein as a substrate for assaying rat MMP-7. This substrate does not require a prerun step or substrate crosslinking to give uniform staining and clear band formation. It is necessary for heparin to run to the same region of the gel as the enzyme to produce its enhancing effect. For MMP-7 movement of heparin and enzyme is almost equal; for the collagenases it is necessary to add heparin to each well after the electrophoretic run is underway. Possible mechanisms of activity enhancement are discussed. (c) 2001 Academic Press.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:786221 CAPLUS
DOCUMENT NUMBER: 134:98498
TITLE: Effects of heparin on the growth, extracellular matrix and matrix metalloproteinase gene expression in rat hepatic stellate cells
AUTHOR(S): Li, Wencai; Zhang, Jinsheng; Huang, Guangeun; Zhu, Hongquang; Zhang, Xiarong; Zhang, Yuee
CORPORATE SOURCE: Dep. Pathology, Shanghai Medical Univ., Shanghai, 20003, Peop. Rep. China
SOURCE: Zhonghua Ganzangbing Zazhi (2000), 8(4), 200-202
CODEN: ZGZZFE; ISSN: 1007-3418
PUBLISHER: Chongqing Yike Daxue, Dier Linchuang Xueyuan
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Objective: To study the effects of heparin on the growth, extracellular matrix and matrix metalloproteinase (MMP) gene expression in rat hepatic stellate cells (HSC). Methods: Activated HSC was treated by heparin or fetal calf serum without heparin. The cell growth was evaluated by actual cell count and BrdU-labeled immunocytochem. stain. The gene expressions of type I and IV procollagen, fibronectin, MMP-2 and membrane type matrix metalloproteinase (MT-MMP) were investigated by immunocytochem. stain and digoxigenin-labeled in situ hybridization technique, resp. In addition, the gelatinase activity of MMP-2 was examined by zymog. Results: Heparin could obviously reduce HSC growth, inhibit the synthesis of type I procollagen and fibronectin protein, and the gene expressions of type I procollagen, fibronectin and MT-MMP. The expressions of type IV procollagen, MMP-2 and MMP-2 activity were not affected by heparin. Conclusion: The results demonstrate that heparin can inhibit HSC proliferation, down-regulate interstitial collagen synthesis and inhibit MT-MMP gene expression.

L9 ANSWER 8 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:688045 CAPLUS
DOCUMENT NUMBER: 133:271734
TITLE: Inhibition of matrix metalloproteinases with polymers and pharmaceutical applications thereof

INVENTOR(S): Marchant, Nancy S.; Dickens, Elmer Douglas, Jr.; Kemp, Shannon M.
PATENT ASSIGNEE(S): The B.F.Goodrich Company, USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056283	A1	20000928	WO 2000-US7158	20000317

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-275314 A 19990324
AB Polymeric compns. and devices for reducing or inhibiting the undesired effects or activity of matrix metalloproteinases (MMPs) in the body. Suitable devices include stents, catheters, guidewires, implants, or similar devices having a polymeric coating capable of inhibiting or countering the activity or effects of matrix metalloproteinases throughout the body. The compns. may further include one or more pharmaceutical agent.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:587694 CAPLUS
DOCUMENT NUMBER: 134:36750
TITLE: Effect of heparin and related glycosaminoglycan on PDGF-induced lung fibroblast proliferation, chemotactic response and matrix metalloproteinases activity
AUTHOR(S): Sasaki, Masahiro; Kashima, Masayuki; Ito, Takefumi; Watanabe, Akiko; Sano, Masaaki; Kagaya, Manabu; Shioya, Takanobu; Miura, Mamoru
CORPORATE SOURCE: Second Department of Internal Medicine, Akita University School of Medicine, Akita, 010, Japan
SOURCE: Mediators of Inflammation (2000), 9(2), 85-91
CODEN: MNFLEF; ISSN: 0962-9351
PUBLISHER: Carfax Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fibroblast migration, proliferation, extracellular matrix protein synthesis and degradation are the key events in various biol. and pathol. processes in pulmonary fibrosis. In addition, biopsy specimens from the lungs of patients with pulmonary fibrosis show increased nos. of mast cells which have metachromatic granules containing heparin, histamin and proteases. Little is known about how these products influence pulmonary fibrosis. In the present study, we investigated the effect of heparin and

related glycosaminoglycans on PDGF-induced lung fibroblast proliferation and chemotactic response in vitro. In addition, we examined the effect of heparin on both the induction of matrix metalloproteinases (MMPs) and MMPs activity in lung fibroblasts in vitro. Heparin, de-N-sulfated heparin but not heparan sulfate inhibited PDGF-induced lung fibroblast proliferation. In contrast, only heparin inhibited PDGF-stimulated human lung fibroblast chemotaxis. Neg. charged poly-L-glutamic acid had no effect on either fibroblast proliferation or chemotaxis. Thus the neg. charge alone cannot account for the antiproliferative and antichemotactic effects of heparin. Furthermore, heparin and heparan sulfate also had no inhibitory effect on induction of MMPs, including MMP-1 (interstitial collagenase), MMP-2 (gelatinase A) and MMP-9 (gelatinase B). Only heparin inhibited both MMP-1 and MMP-2/MMP-9 activity. Addnl., tissue inhibitor of metalloproteinase type 1 (TIMP-1) and type 2 (TIMP-2) inhibited PDGF-stimulated human lung fibroblast chemotaxis. The ability of heparin to inhibit fibroblast chemotaxis may account for the inhibitory effect of heparin on MMP activity. The above results suggested that heparin and related glycosaminoglycans differentially regulate PDGF-induced lung fibroblast proliferation, chemotaxis and MMPs activity and further that these effects may have a key role in extracellular matrix remodeling in inflammatory lung disease.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 45 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:160236 CAPLUS

DOCUMENT NUMBER: 132:291982

TITLE: Epidermal growth factor-like ligands differentially up-regulate matrix metalloproteinase 9 in head and neck squamous carcinoma cells

AUTHOR(S): O-Charoenrat, Pornchai; Modjtahedi, Helmout; Rhys-Evans, Peter; Court, William J.; Box, Gary M.; Eccles, Suzanne A.

CORPORATE SOURCE: Tumor Biology and Metastasis Group, Section of Cancer Therapeutics, The Institute of Cancer Research, Surrey, SM2 5NG, UK

SOURCE: Cancer Research (2000), 60(4), 1121-1128
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: AACR Subscription Office

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Head and neck squamous cell carcinomas (HNSCCs) are characterized by a marked propensity for local invasion and dissemination to cervical lymph nodes, with distant metastases developing in 30-40% of cases. Overexpression of the epidermal growth factor receptor (EGFR/c-erbB-1) and/or its ligands and high levels of certain matrix metalloproteinases (MMPs) have been associated with poor prognosis. The aim of this study was to examine the effects of EGFR ligands on gelatinase expression and invasion in HNSCC cell lines. We tested epidermal growth factor (EGF), transforming growth factor α, betacellulin, heparin-binding EGF, and amphiregulin and measured expression of gelatinases MMP-9 and MMP-2 in an established squamous carcinoma cell line (Detroit-562) and in two cell lines newly derived from patients with head and neck cancers (SIHN-005A and SIHN-006). Incubation of the cell lines with EGF-like ligands up-regulated MMP-9 (but not MMP-2) expression as measured by semiquant. reverse transcription-PCR in a dose-dependent manner, with the effects being most marked in cells with high EGFR levels and undetectable in cells

with low levels. Maximum stimulation was obtained in a concentration range of 10-100 nM. In addition, we confirmed by zymog. that gelatinolytic activity consistent with MMP-9 (Mr 92,000) was up-regulated in parallel with increases in gene expression. Betacellulin (which binds both to EGFR and c-erbB-4 receptors) consistently increased MMP-9 expression and activation to a significantly greater degree than the other four ligands when tested at equimolar concns. In parallel with MMP-9 up-regulation, all EGF-like ligands increased tumor cell invasion through Matrigel in in vitro Transwell assays. These activities were independent of ligand effects on cell proliferation. Antagonist (ICR62) or agonist (ICR9) anti-EGFR monoclonal antibodies, resp., inhibited or potentiated MMP-9 activity and tumor cell invasion induced by all ligands. Furthermore, a monoclonal antibody that neutralizes MMP-9 activity (Ab1) also inhibited ligand-induced invasion of HNSCC. We confirmed that tumor cell lines used in these studies (and a larger series not reported here) generally expressed multiple c-erbB receptors and ligands. These results indicate that autocrine or paracrine signaling through EGFR potentiates the invasive potential of HNSCC via the selective up-regulation and activation of MMP-9. Furthermore, ligands such as betacellulin (which is commonly expressed in HNSCC), which can bind to and activate other c-erbB receptors, may be especially potent in this regard.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 45 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:727821 CAPLUS

DOCUMENT NUMBER: 132:246062

TITLE: Effect of heparin on the production of matrix metalloproteinases and tissue inhibitors of metalloproteinases by human dermal fibroblasts

AUTHOR(S): Gogly, B.; Dridi, M.; Hornebeck, W.; Bonnefoix, M.; Godeau, G.; Pellat, B.

CORPORATE SOURCE: Laboratory of Physiopathology of Non-Mineralized Tissues, University Rene Descartes Paris V, U.F.R. Odontology, Montrouge, 92120, Fr.

SOURCE: Cell Biology International (1999), 23(3), 203-209
CODEN: CBIIEV; ISSN: 1065-6995

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The influence of heparin and a heparin fragment devoid of anticoagulant activity on the production of matrix metalloproteinases and tissue inhibitors of metalloproteinases by human dermal fibroblasts was studied. Doses (0.1-400 μg/mL) responses were performed and data obtained were similar whatever heparin or fragment was used. The basal expression of collagenase by fibroblasts decreased quasi-linearly with increasing doses of heparins from 1 to 400 μg/mL. TIMP-1 levels were not affected by supplementing serum free culture medium with heparins. On the contrary, at low concentration, i.e. 1-10 μg/mL, heparins stimulated the secretion of both 72-kDa gelatinase (1.4-1.6-fold) and particularly TIMP-2 (>4-fold). At high doses, MMP-2 and TIMP-2 production by fibroblasts returned to basal levels. These results suggested that the local concentration of heparin released by mast cells could be instrumental in modulating fibroblast growth and proteolytic phenotype. (c) 1999 Academic Press.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:336109 CAPLUS
DOCUMENT NUMBER: 131:128451
TITLE: Acidic fibroblast growth factor induces an antifibrogenic phenotype in human lung fibroblasts
AUTHOR(S): Becerril, Carina; Pardo, Annie; Montano, Martha; Ramos, Carlos; Ramirez, Remedios; Selman, Moises
CORPORATE SOURCE: Instituto Nacional de Enfermedades Respiratorias, Universidad Nacional Autonoma de Mexico, Mexico, Mex.
SOURCE: American Journal of Respiratory Cell and Molecular Biology (1999), 20(5), 1020-1027
CODEN: AJRBEL; ISSN: 1044-1549
PUBLISHER: American Lung Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acidic fibroblast growth factor (FGF-1), a prototype member of the heparin-binding growth factor family, influences proliferation, differentiation, and protein synthesis in different cell types. However, its possible role on lung extracellular matrix (ECM) metabolism has not been evaluated. Here, the authors examined the effects of FGF-1 and FGF-1 plus heparin on type I collagen, collagen-binding stress protein HSP47, interstitial collagenase (matrix metalloproteinase [MMP]-1), gelatinase A, and tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 expression by normal human lung fibroblasts. Heparin was used because it enhances the biol. activities of FGF-1. Fibroblasts were exposed either to 20 ng/mL FGF-1 plus 100 μg/mL heparin for 48 h or to FGF-1 or heparin alone. MRNA expression was analyzed by Northern blot. Collagen synthesis was evaluated by digestion of [3H]collagen with bacterial collagenase, MMP-1 by Western blot, and gelatinolytic activities by zymog. The results show that FGF-1 induced collagenase mRNA expression, which was strongly enhanced when FGF-1 was used with heparin. Likewise, both FGF-1 and FGF-1 plus heparin reduced by 70-80% the expression of type I collagen transcript, in part via effect on pro-α1(I) collagen mRNA stability. A downregulation of HSP47 gene expression was also observed Synthesis of collagen and collagenase proteins paralleled gene expression results. FGF-1 activities were abolished with genistein, a tyrosine kinase inhibitor. Neither FGF-1 nor FGF-1 plus heparin affected the expression of TIMP-1, TIMP-2, and gelatinase A. Thus, FGF-1, mostly in the presence of heparin, upregulates collagenase and downregulates type I collagen expression that might have a protective role in avoiding collagen accumulation during lung ECM remodeling.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:760794 CAPLUS
DOCUMENT NUMBER: 130:134148
TITLE: Influence of heparin(s) on the interleukin-1-β-induced expression of collagenase, stromelysin-1, and tissue inhibitor of metalloproteinase-1 in human gingival fibroblasts
AUTHOR(S): Gogly, Bruno; Hornebeck, William; Groult, Nicole; Godeau, Gaston; Pellat, Bernard
CORPORATE SOURCE: Laboratory of Biology and Physiopathology, U.F.R. Odontology, University Rene Descartes, Montrouge, 92120, Fr.

SOURCE: Biochemical Pharmacology (1998), 56(11), 1447-1454
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Here, the authors describe the influence of heparin(s) on the interleukin-1-β (IL-1 β)-induced expression of collagenase (matrix metalloproteinase-1, MMP-1), stromelysin-1 (matrix metalloproteinase-3, MMP-3) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) in human gingival fibroblasts (HGF). Amts. of secreted enzymes and inhibitors as well as their mRNA steady-state levels increased significantly following supplementation of HGF culture medium with 2 ng/mL of IL-1 β. Addition of heparin to cell culture medium 1 h following IL-1 β decreased MMP and TIMP-1 expression in a dose-dependent manner. The inhibitory effect of heparin was significant at a concentration as low as 1 μg/mL. These findings could be reproduced with a low Mr heparin fragment devoid of anticoagulant activity. Heparin and fragments might therefore reduce the excessive proteolytic capacity of the gingival fibroblast during inflammation and could be useful as pharmacol. agent(s) in gingivitis and periodontitis.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 45 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:400791 CAPLUS
DOCUMENT NUMBER: 129:160116

TITLE: Collagenase-3 (matrix metalloproteinase- 13) expression is induced in oral mucosal epithelium during chronic inflammation

AUTHOR(S): Uitto, Veli-Jukka; Airola, Kristiina; Vaalamo, Maarit; Johansson, Nina; Putnins, Edward E.; Firth, James D.; Salonen, Jukka; Lopez-Otin, Carlos; Saarialho-Kere, Ulpu; Kahari, Veli-Matti
CORPORATE SOURCE: Department of Oral Biological and Medical Sciences, University of British Columbia, Vancouver, BC, V6T 1Z3, Can.

SOURCE: American Journal of Pathology (1998), 152(6), 1489-1499
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Increased proliferation of mucosal epithelium during inflammation is associated with degradation of subepithelial connective tissue matrix and local invasion of the epithelial cells. Here we have studied, whether collagenase-3 (MMP-13), a collagenolytic matrix metalloproteinase with an exceptionally wide substrate specificity, is expressed in the epithelium of chronically inflamed mucosa. Examination of human gingival tissue sections from subjects with chronic adult periodontitis with in situ hybridization revealed marked expression of MMP-13 in basal cells of some epithelial rete ridges expanding into connective tissue. Immunohistochem. staining demonstrated that these cells also expressed strongly laminin-5, suggesting that they are actively migrating cells. A strong signal for MMP-13 mRNA was occasionally also noted in the suprabasal epithelial cells facing the gingival pocket, whereas no collagenase-1 (MMP-1) mRNA was detected in any areas of the epithelium. MMP-13 expression was also detected in fibroblast-like cells associated with collagen fibers of the

inflamed subepithelial connective tissue. In organ culture of human oral mucosa, MMP-13 mRNA expression was observed in epithelial cells growing into connective tissue of the specimens. Regulation of MMP-13 expression was examined in cultured normal nonkeratinizing epithelial cells isolated from porcine periodontal ligament. In these cells, MMP-13 expression at the mRNA and protein level was potently enhanced (up to sixfold) by tumor necrosis factor-α, transforming growth factor-β1, and transforming growth factor-α and by keratinocyte growth factor in the presence of heparin. In addition, plating periodontal ligament epithelial cells on type I collagen stimulated MMP-13 expression (sevenfold) as compared with cells grown on tissue culture plastic. The results of this study show, that expression of MMP-13 is specifically induced in undifferentiated epithelial cells during chronic inflammation due to exposure to cytokines and collagen. Thus, it is likely that MMP-13 expression is instrumental in the subepithelial collagenolysis and local invasion of the activated mucosal epithelium into the connective tissue.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 15 OF 45 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:237651 CAPLUS
DOCUMENT NUMBER: 126:258951
TITLE: Effect of glucose and heparin on mesangial α1 (IV) COLL and MMP-2/TIMP-2 mRNA expression
AUTHOR(S): Caenazzo, C.; Garbisa, S.; Onisto, M.; Zampieri, M.; Baggio, B.; Gambaro, G.
CORPORATE SOURCE: Institute of Histology and Embriology, Medical School, Padua, 35121, Italy
SOURCE: Nephrology, Dialysis, Transplantation (1997), 12(3), 443-448
CODEN: NDTREA; ISSN: 0931-0509
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mesangial cells are responsible for the synthesis of mesangial matrix as well as its degradation, which is mediated by a number of proteolytic activities, including metalloproteinases (MMPs). Imbalanced matrix protein metabolism may be responsible for mesangial expansion and glomerulosclerosis in diabetic nephropathy. Heparin prevents this complication. In human and murine mesangial cell cultures, RT-PCR was able to detect mRNA expression for a number of mols. involved in the mesangial extracellular matrix turnover: type IV collagen [α1 (IV)COLL], MMP-1, MMP-2, MMP-3, MMP-9 and MMP-10, and the tissue inhibitors TIMP-1 and TIMP-2. The expression of mRNA for α1 (IV)COLL and MMP-2/TIMP-2 balance was studied in human cells in the presence of high glucose and heparin. MRNAs for all the studied mols. were expressed at different levels. Interestingly, a shift in the balance of α1 (IV)COLL, MMP-2 and TIMP-2 was observed in high glucose, which was partially reversed by heparin supplementation. The new equilibrium was mostly due to the down-regulation of type IV collagen expression, rather than further reduction of potential proteolysis. Our data, while extending the list of potential mediators of mesangial matrix catabolism, highlight a mol. mechanism by which the pathogenesis of diabetic nephropathy may be sustained, and at the same time suggest that heparin may have the potential to correct this abnormality.

L9 ANSWER 16 OF 45 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:196235 CAPLUS
DOCUMENT NUMBER: 126:289936
TITLE: The hemopexin-like domain (C domain) of human gelatinase A (matrix metalloproteinase-2) requires Ca2+ for fibronectin and heparin binding. Binding properties of recombinant gelatinase A C domain to extracellular matrix and basement membrane components
AUTHOR(S): Wallon, U. Margaretha; Overall, Christopher M.
CORPORATE SOURCE: FacultyDentistry, Dep. Biochem. Mol. Biol., Univ. British Columbia, Vancouver, BC, V6T 1Z3, Can.
SOURCE: Journal of Biological Chemistry (1997), 272(11), 7473-7481
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The binding properties of the COOH-terminal hemopexin-like domain (C domain) of human gelatinase A (matrix metalloproteinase-2, 72-kDa gelatinase) were investigated to determine whether the C domain has binding affinity for extracellular matrix and basement membrane components. Recombinant C domain (rC domain) (Gly417-Cys631) was expressed in Escherichia coli, and the purified protein, identified using two antipeptide antibodies, was determined by electrospray mass spectrometry to have a mass of 25,925 Da, within 0.1 Da of that predicted. As assessed by microwell substrate binding assays and by column affinity chromatog., the matrix protein laminin, denatured type I collagen, elastin, SPARC (secreted protein that is acidic and rich in cysteine), tenascin, and Matrigel were not bound by the rC domain. Unlike the hemopexin-like domains of collagenase and stromelysin, the rC domain also did not bind native type I collagen. Nor were native or denatured types VII collagen bound. However, binding to heparin and fibronectin (Kd, 1.1+10-6 M) could be disrupted by 0.58-0.76 and 0.3 M NaCl, resp. Using nonoverlapping chymotrypsin-generated fragments of fibronectin, binding sites for the rC domain were found on both the 40-kDa heparin binding and the 120-kDa cell binding fibronectin domains (Kd values, .apprx.4-6+10-7 M). The Ca2+ ion, but not the potential structural Zn2+ ion, were found to be essential for maintaining the binding properties of the protein. The apo-form of the rC domain did not bind heparin, and both EDTA and the specific Ca2+ ion chelator 1,2-bis(2-aminophenoxy) ethane-N,N,N',N'-tetraacetic acid, but not the Zn2+ ion chelator 1,10-phenanthroline, eluted the holo form of the rC domain from both heparin-Sepharose and fibronectin. Inductive coupled plasma mass spectrometry also did not detect a Zn2+ ion in the rC domain. In contrast, reduction with 65 mM dithiothreitol did not interfere with heparin binding, further emphasizing the crucial structural role played by the Ca2+ ion. Together, these data demonstrate for the first time that the hemopexin-like domain of gelatinase A has a binding site for fibronectin and heparin, and that Ca2+ ions are important in maintaining the structure and function of the domain.

L9 ANSWER 17 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:141789 CAPLUS
DOCUMENT NUMBER: 126:223430
TITLE: Differential regulation of extracellular matrix metalloproteinase and tissue inhibitor by heparin and cholesterol in fibroblast cells

AUTHOR(S): Tyagi, Suresh C.; Kumar, Suresh; Katwa, Laxmansa
CORPORATE SOURCE: Medical Center, University of Mississippi, Jackson, MS, 39216-4505, USA
SOURCE: Journal of Molecular and Cellular Cardiology (1997), 29(1), 391-404
CODEN: JMCDAY; ISSN: 0022-2828
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Heparin has been shown to stimulate angiogenesis in the border zones surrounding infarcted myocardium. Matrix metalloproteinases (MMP), which are involved in extracellular matrix (ECM) organization, have also been shown to be activated. Cholesterol is required for receptor signaling in the plasma membrane, but a role of MMPs for cholesterol in ECM remodeling has not yet been shown. To examine whether heparin and cholesterol induce MMP and tissue inhibitor of metalloproteinase (TIMP) in human heart fibroblast (HHF) cells, confluent HHF cells were treated with cholesterol (100 μM) or heparin (20 μM). MMP activity was measured using zymog. and TIMP was measured by Western blot anal. The number of HHF cells, measured by a hemocytometer, increased after heparin or cholesterol treatment. Gelatinase A (MMP-2) activity increased in heparin treated cells, and the TIMP-1 level increased in cholesterol-treated cells. Based on Northern blot anal., we observed that both MMP-1 and MMP-2 were induced at the gene transcription level by heparin and that TIMP-1 was induced by cholesterol. To examine whether the effects of heparin and cholesterol were due to Ca2+ mobilization, we carried out Ca2+ transient assays using FURA-2/AM as a fluorescence probe in HHF cells. Heparin induced a slow rise in the Ca2+ transient with a slow decay, and cholesterol induced a rapid rise with a slow reversal to the baseline calcium level. This suggested that the effect of heparin on Ca2+ release from HHF may be secondary to the receptor binding on the cell membrane but that cholesterol may have a direct effect. Protein kinase inhibitor and Ca2+-channel blocker have been shown to inhibit MMP expression. To examine whether the effect of heparin on MMP expression is mediated through the collagenase promoter activity, we carried out gel-shift assays using a 21-oligonucleotide analog to the MMP-1 promoter sequence. Results suggested that the increase in MMP promoter activity by heparin is due to a specific transcription factor binding to MMP-1 promoter sequence. The effect of cholesterol on fibroblast cell proliferation is due to the tissue inhibitor. This study demonstrated the role of heparin and cholesterol in ECM remodeling and has implications for angiogenesis and atherosclerosis, resp.

L9 ANSWER 18 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:640640 CAPLUS
DOCUMENT NUMBER: 125:268821
TITLE: What kind of specimen should be selected for determining tissue inhibitor of metalloproteinase-1 (TIMP-1) in blood?
AUTHOR(S): Jung, Klaus; Nowak, Lars; Lein, Michael; Henke, Wolfgang; Schnorr, Dietmar; Loening, Stefan A.
CORPORATE SOURCE: Department of Urology, Humboldt University Berlin, Berlin, D-10098, Germany
SOURCE: Clinica Chimica Acta (1996), 254(1), 97-100
CODEN: CCATAR; ISSN: 0009-8981
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal

LANGUAGE: English
AB Blood serum is not appropriate to provide reliable data of TIMP-1 for diagnostic purposes because elevations of TIMP-1 during specimen preparation are unspecific. Heparin plasma is the specimen of choice and should be used rather than EDTA plasma since EDTA as anticoagulant does not exclude the obviously unspecific elevations of both TIMP-1 and metalloproteinase concns.

L9 ANSWER 19 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:480815 CAPLUS
DOCUMENT NUMBER: 125:162638
TITLE: Growth factor induction of epithelial cell proliferation and matrix metalloproteinase secretion (thymidine, heparin, heparan sulfate, kgf)
AUTHOR(S): Putnins, Edward Ewald
CORPORATE SOURCE: Univ. of British Columbia, Vancouver, BC, Can.
SOURCE: (1995) 171 pp. Avail.: Univ. Microfilms Int., Order No. DANN06046.
From: Diss. Abstr. Int., B 1996, 57(3), 1735
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L9 ANSWER 20 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:337257 CAPLUS
DOCUMENT NUMBER: 125:54278
TITLE: Stimulation of collagenase (matrix metalloproteinase-1) synthesis in histiotypic epithelial cell culture by heparin is enhanced by keratinocyte growth factor
AUTHOR(S): Putnins, Edward E.; Firth, James D.; Uitto, Veli-Jukka
CORPORATE SOURCE: Dep. of Oral Biology, Univ. of British Columbia, Vancouver, BC, Can.
SOURCE: Matrix Biology (1996), 15(1), 21-29
CODEN: MTBOEC; ISSN: 0945-053X
PUBLISHER: Fischer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of heparin and heparan sulfate in the control of epithelial collagenase production was investigated utilizing a histiotypic cell culture model. The effect of keratinocyte growth factor (KGF), a heparin-binding growth factor, on collagenase secretion was also examined Heparin, and, to a lesser extent, heparan sulfate induced release of a 58-kDa, gelatin-degrading enzyme which was subsequently identified as the collagenase, matrix metalloproteinase-1. The increase in collagenase secretion by heparin was further enhanced by the addition of KGF. KGF alone did not have any effect. Anal. of secreted radiolabeled proteins showed that the increase in collagenase activity was not due to a general increase in protein synthesis. Synthesis of collagenase protein was specifically increased by heparin and further increased by KGF plus heparin. Heparin and heparan sulfate in combination with KGF may thus have important roles in the regulation of epithelial cell collagenase under conditions such as inflammation and wound healing.

L9 ANSWER 21 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:674888 CAPLUS
DOCUMENT NUMBER: 123:189212

TITLE: Keratinocyte growth factor stimulation of gelatinase (matrix metalloproteinase-9) and plasminogen activator in histiotypic epithelial cell culture
AUTHOR(S): Putnins, Edward E.; Firth, James D.; Uitto, Veli-Jukka
CORPORATE SOURCE: Faculty of Dentistry, University of British Columbia, Vancouver, BC, Can.
SOURCE: Journal of Investigative Dermatology (1995), 104(6), 989-94
CODEN: JIDEAE; ISSN: 0022-202X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this investigation was to examine the role that keratinocyte growth factor (KGF) plays in the control of matrix-degrading protease activity in epithelial cells. The culture conditions had a significant effect on cellular responses to the growth factor. In histiotypic culture on porous-polycarbonate membranes, porcine periodontal ligament epithelial cells responded to KGF with increased 92-kDa gelatinase (matrix metalloproteinase [MMP]-9) activity. No such response was observed in cells maintained on plastic plates. Epidermal growth factor and platelet-derived growth factor also increased MMP-9 activity in the histiotypic cultures of epithelial cells. Addition of heparin with KGF produced a further increase in MMP-9 activity, with heparin alone having no effect. Precoating of polycarbonate membranes with matrix components showed that fibronectin and an engineered poly-RGD mol. substrate were required for KGF plus heparin to increase MMP-9 activity. Precoating plastic culture plates with the same proteins did not generate the same response. Concomitant with gelatinase activity, KGF also increased urokinase-type plasminogen activator in the epithelial cells. Thus, KGF appears to be an important regulator of protease secretion in epithelial cells.

L9 ANSWER 22 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:645998 CAPLUS
DOCUMENT NUMBER: 123:109421
TITLE: Collagen and collagenase mRNAs in normal and sclerotic glomeruli: predictors of progression and response to therapy
AUTHOR(S): He, Ci-Jiang; Yang, Chih-Wei; Peten, Emmanuel P.; Liu, Zhi-Hong; Patel, Anita; Striker, Liliane J.; Striker, Gary E.
CORPORATE SOURCE: Renal Cell Biology Section, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, USA
SOURCE: Kidney International, Supplement (1995), 49, S39-S43
CODEN: KISUDF; ISSN: 0098-6577
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Progressive glomerulosclerosis is associated with decreasing kidney function, eventuating in end-stage renal failure. There are multiple components of the extracellular matrix, and the exact composition in various renal diseases is not known. Thus, we examined some of the major components of the extracellular matrix (ECM) in murine and human glomerular diseases. We studied matrix synthesis and degradation at the level of gene expression and ECM composition in the intact glomerulus. To determine whether the composition of
sclerosis was similar among diseases, we examined a normal mouse strain and compared it with strains which spontaneously developed glomerulosclerosis.

The baseline levels of matrix components varied between different mouse strains, and this level correlated with their propensity to develop glomerulosclerosis. In addition, when glomerulosclerosis was induced, the baseline ECM mRNA level predicted the subsequent outcome. We studied mice transgenic for bovine growth hormone, since they develop progressive glomerulosclerosis. Treatment with heparin substantially decreased the lesions without changes in type IV collagen mRNAs. However, there was an up-regulation of both the mRNA and enzyme activity for the 92 kD matrix metalloproteinase. In contrast, when these mice were treated with either angiotensin converting enzyme inhibitors or angiotensin II (Ang II) receptor antagonists, the glomerulosclerosis was accentuated histol. and the ECM synthetic and degradative mRNAs were elevated. These data suggest that the mRNA levels reflect response to therapy. We examined glomeruli from human nephrectomy specimens and found an increase in the mRNA levels for both the synthetic and degradative components of the ECM in those specimens with glomerulosclerosis. Preliminary examination of glomeruli isolated from renal biopsies reveals homogeneity in the α2/α3IV ratio among diabetics, but not among those with IgA nephropathy. These data suggest that modifications in ECM gene regulation may serve as predictors of progression.

L9 ANSWER 23 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:695795 CAPLUS
DOCUMENT NUMBER: 121:295795
TITLE: Reciprocated matrix metalloproteinase activation: A process performed by interstitial collagenase and progelatinase A
AUTHOR(S): Crabbe, Thomas; O'Connell, James P.; Smith, Bryan J.; Docherty, Andrew J. P.
CORPORATE SOURCE: Department of Oncology, Celltech Research, Slough, SL1 4EN, UK
SOURCE: Biochemistry (1994), 33(48), 14419-25
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Gelatinase A, a member of the matrix metalloproteinase (MMP) family, is secreted possessing an 80 amino acid N-terminal propeptide that must be removed to generate the active enzyme. Purified progelatinase A was activated to 38% of maximum by a 6 h incubation at 37° with equimolar concns. of trypsin-activated interstitial collagenase (another MMP). The increase in activity was accompanied by cleavage of the Mr 72 000 progelatinase A to the Mr 66 000 active enzyme that has Y81 as its N-terminus. At low concns., progelatinase A was processed via an inactive intermediate, suggesting that its activation is a biphasic process. This was confirmed by the action of collagenase on proE375→A (a mutant of progelatinase A that cannot become active) because, in this instance, only an Mr 68 000 species with L38 as the N-terminus was produced. The remaining propeptide amino acids to Y81 could be readily removed by added active gelatinase A, indicating that collagenase works by generating an intermediate that is susceptible to autolytic activation. Although relatively slow, the rate of activation could be increased approx. 10-fold by the addition of 100 μg/mL heparin. This binds to the C-terminal domain of collagenase and progelatinase A and presumably acts as a template that positions the reactants close to one another. Collagenase activated by trypsin retains 8 or 14 amino acids of its propeptide. The activated gelatinase A was able to remove these by cleaving the Q80-F81 peptide bond, an event that has been shown to significantly increase the activity

of collagenase against fibrillar collagen. The fact that the complete degradation of native collagen requires the activities of both a collagenase and a gelatinase provides a functional basis for this reciprocated mechanism of activation.

L9 ANSWER 24 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:628552 CAPLUS
DOCUMENT NUMBER: 121:228552
TITLE: Angiogenic potential in vivo by Kaposi's sarcoma cell-free supernatants and HIV-1 tat product: inhibition of KS-like lesions by tissue inhibitor of metalloproteinase-2
AUTHOR(S): Albini, Adriana; Fontanini, Gabriella; Masiello, Luciana; Tacchetti, Carlo; Bigini, Daniela; Luzzi, Paola; Noonan, Douglas M.; Stetler-Stevenson, William G.
CORPORATE SOURCE: National Institute Research Cancer, Genoa, Italy
SOURCE: AIDS (London, United Kingdom) (1994), 8(9), 1237-44
CODEN: AIDSET; ISSN: 0269-9370
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors studied the neoplastic nature of Kaposi's sarcoma (KS). A highly vascularized lesion, KS is frequently associated with AIDS, indicating HIV products may be involved. The authors determined the angiogenic properties of KS cell-secreted products and the HIV-1-tat gene product in vivo. Cell-free secreted products (KS-CM) from cultured epidemic and sporadic KS spindle cells or recombinant (r) HIV-1 tat protein were injected into mice with a matrix support (Matrigel). KS-CM produced lesions carrying all the phenotypic hallmarks of KS, as observed by light and electron microscopy: spindle-shaped cells, hemorrhages and an inflammatory infiltrate, as well as Factor VIII-pos. endothelial cells lining new blood vessels. Electron microscopy indicated an initial granulocyte invasion, with spindle-cell migration and neocapillary formation in the center of the matrix. These lesions required the cofactor heparin; KS-CM or heparin alone were poorly angiogenic. A less intense angiogenesis, with lower cellularity and few granulocytes, was observed in basic fibroblast growth factor (bFGF)/heparin lesions, indicating that factors other than bFGF are present in the KS spindle-cell products. When the collagenase inhibitor tissue inhibitor of metalloproteinases (TIMP)-2 was added to the sponges, KS-CM-induced angiogenesis was reduced by approx. 65% and bFGF-induced angiogenesis inhibited completely. Recombinant HIV-1 tat protein, a growth factor for KS cells, induced vascularization that was also enhanced by heparin, implying that HIV-1 tat could contribute to the etiol. of HIV-associated KS. KS-like lesions were obtained by injecting cell-free secreted products, suggesting that KS is a self-propagating proliferative lesion caused by a cytokine imbalance and not a true neoplasm. Heparin-binding factors appear to be involved and HIV-1 tat angiogenic properties implicate this mol. in AIDS-associated KS. Inhibition of KS-CM-induced KS-like lesions by TIMP-2 suggests that metalloproteinase inhibitors could be potential therapeutic agents for KS.

L9 ANSWER 25 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:595476 CAPLUS
DOCUMENT NUMBER: 121:195476
TITLE: Heparin selectively inhibits gene expression of matrix metalloproteinase transin in cultured mesangial cells
AUTHOR(S): Kitamura, Masanori; Maruyama, Naoki; Mitarai, Tetsuya;

Nagasawa, Ryuji; Yokoo, Takashi; Sakai, Osamu
CORPORATE SOURCE: School of Medicine, Jikei University, Tokyo, Japan
SOURCE: Biochemical and Biophysical Research Communications (1994), 203(2), 1333-8
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study is to examine the transcriptional regulation of matrix metalloproteinase transin in glomerular mesangial cells responding to inflammatory cytokines and heparin. Northern blot anal. revealed that IL-1β preferentially induced transin mRNA. The stimulatory effect was not specific to transin, and upregulation of procollagen α1(IV), laminin B2 and tissue inhibitor of metalloproteinases-1 (TIMP-1) mRNAs was also observed After IL-1 stimulation, expression of the transin transcript increased progressively for up to 48 h, differing from the limited induction of procollagen α1(IV) or TIMP-1. When mesangial cells were stimulated by IL-1β in the presence of heparin, transin expression was markedly suppressed in a dose-dependent manner. The inhibitory effect f heparin was specific to transin, and induction of procollagen α1(IV), laminin B2 or TIMP-1 by IL-1β was not affected. These findings revealed the selective counter regulation by IL-1β and heparin of the transin expression in mesangial cells.

L9 ANSWER 26 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:400501 CAPLUS
DOCUMENT NUMBER: 121:501
TITLE: Heparin inhibits the induction of three matrix metalloproteinases (stromelysin, 92-kD gelatinase, and collagenase) in primate arterial smooth muscle cells
AUTHOR(S): Kenagy, Richard D.; Nikkari, Seppo T.; Welgus, Howard G.; Clowes, Alexander W.
CORPORATE SOURCE: Dep. Surg., Univ. Washington, Seattle, WA, 98195, USA
SOURCE: Journal of Clinical Investigation (1994), 93(5), 1987-93
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Heparin inhibits the migration and proliferation of arterial smooth muscle cells and modifies the extracellular matrix. These effects may be the result of heparin's effects on proteinases that degrade the matrix. The authors have previously reported that heparin inhibits the induction of tissue-type plasminogen activator and interstitial collagenase mRNA. The authors have investigated the possibility that heparin affects other members of the matrix metalloproteinase family. Phorbol ester increased the levels of mRNA of collagenase, 92-kD gelatinase and stromelysin as well as the synthesis of these proteins. These effects were inhibited by heparin, but not by other glycosaminoglycans, in a dose-dependent manner. The induction of these matrix metalloproteinases was also inhibited by staurosporine and pretreatment with phorbol ester indicating the involvement of the protein kinase C pathway. In contrast, the 72-kD gelatinase was expressed constitutively and was not affected by phorbol ester or heparin. Tissue inhibitor of metalloproteinases-1 was expressed constitutively and was slightly increased by phorbol ester. It was not affected by heparin. Thus, heparin inhibits the production of four proteinases (tissue plasminogen activator, collagenase, stromelysin and 92-kD gelatinase) that form an interdependent system capable of degrading all the major components of the extracellular matrix.

L9 ANSWER 27 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:4692 CAPLUS
DOCUMENT NUMBER: 118:4692
TITLE: Effects of spermine on water absorption, polyethylene glycol 4000 permeability and collagenase activity in rat descending colon in vivo
AUTHOR(S): Mendizabal, M. V.; Naftalin, R. J.
CORPORATE SOURCE: Div. Biomed. Sci., King's Coll., London, WC2R 2LS, UK
SOURCE: Clinical Science (1992), 83(4), 417-23
CODEN: CSCIAE; ISSN: 0143-5221
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Spermine (5 mM) decreased fluid absorption from 48.83 to 23.98 μL h-1 cm-2; PEG 4000 permeability was increased from 0.030 to 0.047 cm/h and luminal collagenase activity increased from a negligible control value to 250 units/mL. Spermine also caused edema formation within the mucosal interstitial fluid, without inducing an overt breakdown of the mucosa at the luminal surface. Polyamine-free dialyzed seminal plasma had no effect on PEG 4000 permeability, although it still caused a decrease in colonic fluid absorption from 48.83 (control) to 31.41 μL h-1 cm-2. Low-mol.-mass heparin (600 units/mL) prevented the spermine (5 mM)- and whole-semen-induced increase in colonic PEG 4000 permeability and reduced the effect of semen on fluid absorption by 63% and that of spermine by 56%. The Zn2+ chelator and collagenase inhibitor o-phenanthroline reduced the effect of spermine on fluid absorption and PEG 4000 permeability by 100% and on interstitial edema formation. o-Phenanthroline also reduced the effects of whole semen on fluid absorption (by 70%) and on PEG 4000 permeability by 95%. A synthetic peptide inhibitor of mammalian collagenase activity with high affinity reduced the effects of whole semen on PEG 4000 permeability and on fluid absorption in a dose-dependent manner. The inhibitor (2 mM) also reduced the effects of spermine (5 mM) on fluid absorption and PEG 4000 permeability. Apparently, polyamines that are present within semen in the concentration range 5-15 mM act cooperatively with seminal collagenases to disrupt the colonic barrier. Cationic polyamines may activate collagenases by binding to and neutralizing the anionic charge of heparins within the interstitial matrix.

L9 ANSWER 28 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:227979 CAPLUS
DOCUMENT NUMBER: 116:227979
TITLE: Heparin inhibits collagenase gene expression mediated by phorbol ester-responsive element in primate arterial smooth muscle cells
AUTHOR(S): Au, Y. P. Tina; Montgomery, Kevin K.; Clowes, Alexander W.
CORPORATE SOURCE: Dep. Surg., Univ. Washington, Seattle, WA, 98195, USA
SOURCE: Circulation Research (1992), 70(5), 1062-9
CODEN: CIRUAL; ISSN: 0009-7330
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Heparin is a potent inhibitor of arterial smooth muscle cell (SMC) migration and proliferation in vivo and in vitro. It is proposed that heparin affects these SMC functions by interfering with either the expression or the activity of secreted proteases required for cell movement. It has been reported that heparin selectively inhibits the

expression of tissue-type plasminogen activator in SMCs during mitogenesis. This study shows that the gene expression of another kind of protease, interstitial collagenase, is induced by fetal bovine serum and is also suppressed by heparin. The inhibitory effect on the induced collagenase mRNA is specific to heparin-like mols. and does not depend on the anticoagulant activity of heparin. The induction of the collagenase gene depends on the protein kinase C pathway, since it can be induced by phorbol esters such as phorbol 12-myristate 13-acetate and blocked by inhibitors such as H-7 and staurosporine. In transient transfection assays with chloramphenicol acetyltransferase constructs containing the phorbol ester-responsive element introduced into baboon SMCs, heparin inhibits transcription induced by serum or phorbol 12-myristate 13-acetate. These results support the conclusion that, in primate SMCs, interstitial collagenase gene transcription mediated by the phorbol ester-responsive element is blocked by heparin.

L9 ANSWER 29 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:512658 CAPLUS
DOCUMENT NUMBER: 111:112658
TITLE: Mineralization induced by β-glycerophosphate in cultures leads to a marked increase in collagenase synthesis by mouse osteogenic MC3T3-E1 cells under subsequent stimulation with heparin
AUTHOR(S): Sakamoto, S.; Sakamoto, M.; Goldberg, L.; Colarusso, L.; Gotoh, Y.
CORPORATE SOURCE: Lab. Study Connect. Tissue Metab., Harvard Sch. Dent. Med., Boston, MA, 02115, USA
SOURCE: Biochemical and Biophysical Research Communications (1989), 162(2), 773-80
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The clonally derived mouse osteoblast-like cell line MC3T3-E1 was shown to produce latent collagenase (-0.2 units/mL) under stimulation with either heparin or parathormone in confluent cultures. However, MC3T3-E1 cultures which were 1st induced to undergo mineralization by the addition of β-glycerophosphate and were subsequently stimulated with heparin showed an .apprx.10-fold increase in collagenase synthesis. MC3T3-E1 cell collagenase from a small sample of serum-free culture medium was purified 49-fold to a specific activity of 200 units/mg protein with a yield of 14% by heparin-sepharose affinity chromatog. and ion-exchange HPLC. This new mineralization-primed cell culture system may be a valuable model for the study of osteoblast collagenase.

L9 ANSWER 30 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:32167 CAPLUS
DOCUMENT NUMBER: 102:32167
TITLE: Vascular substitute from human placental arteries: glycosaminoglycan and elastin synthesis in the neo-intimal hyperplasia
AUTHOR(S): Moczar, M.; David, P.; Loisance, D.
CORPORATE SOURCE: Fac. Med., CHU Henri Mondor, Creteil, 94 010, Fr.
SOURCE: Life Support Systems (1984), 2(3), 201-8
CODEN: LSSYD6; ISSN: 0261-989X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Long-term evolution of small-diameter vascular substitutes in a heterologous

system was investigated. Heparinized human placental arteries (diameter ≤1 mm) were crosslinked with glutaraldehyde and implanted in infrarenal aortas in rats. Following glutaraldehyde treatment, both pepsin and bacterial **collagenase** were ineffective in hydrolyzing the collagen in the crosslinked arteries. Glycosaminoglycans (GAG) and elastins were metabolically labeled in vitro with [3H]glycosamine and [3H]valine, resp. At 1 yr, heparin [**9005-49-6**] was the major [3H]GAG component. [3H]hyaluronic acid [9004-61-9] accounted for 13% of the total [3H]GAGs. The ratio of chondroitin 4-sulfate [24967-93-9] to chondroitin 6-sulfate [25322-46-7] was higher in the neointima than in the host aorta. A relative increase of the radioactivity in sulfated GAGs occurred from 3 mo to 1 yr. With elastin, at 3 mo following vascular replacement, the neointima was not recovered in sufficient amts. to enable the incorporation of radioactive valine into elastin to be investigated. The samples of neointima and host aorta excised at 1 yr were incubated with [3H]valine, and the [3H]valylproline dipeptides were separated by TLC. The radioactivity eluted at the position of [3H]valylproline residues expressed on a basis of the collagen content of the sample.

L9 ANSWER 31 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:486275 CAPLUS
DOCUMENT NUMBER: 101:86275
TITLE: The interaction of platelet proteins with three fibroblast-derived collagenases
AUTHOR(S): Pisoni, Ronald; Ciaglowski, Raymond E.; Brown, Ray K.; Walz, Daniel A.
CORPORATE SOURCE: Sch. Med., Wayne State Univ., Detroit, MI, 48201, USA
SOURCE: Thrombosis Research (1984), 35(2), 159-68
CODEN: THBRAA; ISSN: 0049-3848
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Three collagenases were purified from the culture medium of human skin fibroblasts by using (NH4)2SO4 fractionation, ion-exchange chromatog., and gel filtration. The cationic collagenase had a mol. weight of 42,000; 2 anionic collagenases had mol. wts. of 63,000 and 115,000. Preincubation of the individual collagenases with bovine low-heparin-affinity platelet protein (β-thromboglobulin) resulted in the inhibition of the 2 anionic activities. Such inhibition was dose-dependent at the microgram level, was not antagonized by heparin, and persisted even when the collagenases had been transformed into their 53,000-mol.-weight forms through treatment with p-aminophenylmercuric acetate. Neither human nor bovine high-heparin-affinity platelet factors (platelet factor 4) nor human β-thromboglobulin were inhibitory to any of the 3 collagenases studied. Apparently, the ability of platelet proteins to inhibit collagenase is specifically influenced by the ionic nature of the enzyme, and this inhibition is specifically dependent upon the type and species source of platelet protein.

L9 ANSWER 32 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:187844 CAPLUS
DOCUMENT NUMBER: 100:187844
TITLE: Isolation and characterization of collagenase synthesized by mouse bone cells in culture
AUTHOR(S): Sakamoto, Seizaburo; Sakamoto, Masako
CORPORATE SOURCE: Lab. Study Connect. Tissue Metab., Harvard Sch. Dent. Med., Boston, MA, 02115, USA
SOURCE: Biomedical Research (1984), 5(1), 39-45

CODEN: BRESD5; ISSN: 0388-6107
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Latent collagenase was isolated by heparin-Sepharose affinity chromatog. from the culture medium of isolated mouse bone cells. Collagenase was synthesized by osteoblast-like cells rather than by osteoclastic cells. Collagenase synthesis by osteoblast-like cells was significantly stimulated by the addition of parathyroid hormone and/or heparin to the culture medium at concns. that induce bone resorption in bone organ culture systems. The cellular origin of the isolated collagenase was confirmed by demonstrating the characteristic 3/4 and 1/4 fragments of collagem α chains, as well as inhibition of the enzyme by anti-mouse bone collagenase antibody.

L9 ANSWER 33 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:154293 CAPLUS
DOCUMENT NUMBER: 100:154293
TITLE: Immunocytochemical localization of collagenase in isolated mouse bone cells
AUTHOR(S): Sakamoto, Masako; Sakamoto, Seizaburo
CORPORATE SOURCE: Lab. Study Connect. Tissue Metab., Harvard Sch. Dent. Med., Boston, MA, 02115, USA
SOURCE: Biomedical Research (1984), 5(1), 29-38
CODEN: BRESD5; ISSN: 0388-6107
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Immunoreactive collagenase was localized in isolated mouse bone cells by indirect immunofluorescent and immunoperoxidase antibody techniques using goat anti-mouse bone collagenase antibody. Immunoreactive collagenase was localized primarily in osteoblast-like cells based on biochem. parameters, i.e., cAMP production and alkaline and acid phosphatase activity changes in response to parathyroid hormone. There was no collagenase immunofluorescence in cell populations rich in osteoclastic cells. Both parathyroid hormone and heparin appeared to stimulate the synthesis and(or) release of immunoreactive collagenase by isolated osteoblast-like cells. Collagenase immunofluorescence of isolated bone cells was observed initially as fine granular fluorescence packed at perinuclear regions. This fine granular fluorescence then appeared to diffuse through the cytoplasm and to be secreted extracellularly.

L9 ANSWER 34 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:580719 CAPLUS
DOCUMENT NUMBER: 95:180719
TITLE: Heparin and bone metabolism: effects of heparin on bone collagenase release and activity and an application of heparin-Sepharose affinity chromatography for in vitro study of bone resorption
AUTHOR(S): Sakamoto, Seizaburo; Sakamoto, Masako
CORPORATE SOURCE: Harvard Sch. Dent. Med., Harvard Med. Sch., Boston, MA, USA
SOURCE: Developments in Biochemistry (1981), 12(Chem. Biol. Heparin), 133-42
CODEN: DEBIDR; ISSN: 0165-1714
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Heparin [**9005-49-6**] stimulated the release of **collagenase** [9001-12-1] from mouse and chick bone cultures and

increased the activity of heparin-induced enzyme when assayed using collagen in the solid state as the substrate. The heparin-induced bone **collagenase** formed a complex with heparin. A heparin-Sepharose 4B gel chromatog. was used to isolate the enzyme from resorbing bone culture medium containing serum and tissue **collagenase** inhibitors. The amount of collagenase activity in the medium correlated with the extent of bone resorption under the specific conditions.

L9 ANSWER 35 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:100478 CAPLUS
DOCUMENT NUMBER: 94:100478
TITLE: Immunoreactive collagenase and bone resorption
AUTHOR(S): Francois-Gillet, Chantal; Delaisse, Jean Marie; Eeckhout, Yves; Vaes, Gilbert
CORPORATE SOURCE: Int. Inst. Cell. Mol. Pathol., Univ. Louvain, Bruxelles, B1200, Belg.
SOURCE: Biochimica et Biophysica Acta (1981), 673(1), 1-9
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Active mouse bone collagenase was excluded from its inhibitory antibody by preincubation of that antibody with various forms of inactive enzyme, e.g. procollagenase, some collagenase-inhibitor complexes, or partially denatured or degraded collagenase. This property allowed the detection of several enzymically inactive forms of collagenase. The accumulation of immunoreactive collagenase in the culture fluid of mouse bones occurred only in the presence of heparin and was not correlated with bone resorption induced by parathyroid hormone. Possibly, the critical role in the resorption of the organic matrix of these explants may be due to another enzyme system than collagenase.

L9 ANSWER 36 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1979:414153 CAPLUS
DOCUMENT NUMBER: 91:14153
TITLE: Collagenase, procollagenase and bone resorption. Effects of heparin, parathyroid hormone and calcitonin
AUTHOR(S): Lenaers-Claeys, Genevieve; Vaes, Gilbert
CORPORATE SOURCE: Lab. Chim. Physiol., Univ. Louvain, Brussels, B-1200, Belg.
SOURCE: Biochimica et Biophysica Acta (1979), 584(3), 375-88
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The addition of heparin [**9005-49-6**] to the culture fluid of mouse tibiae or calvaria did not cause any significant resorption of bone collagen or mineral. However, heparin (or analog sulfated polyanions), enhanced greatly the amount of latent, trypsin-activatable **collagenase** (i.e. procollagenase [39287-99-5]) released by the bones in the medium without influencing that of directly active **collagenase** [9001-12-1] which was always very low. Heparin appeared to act by increasing the production of the enzyme which is immediately excreted. Parathyroid hormone [9002-64-6] induced in the explants a resorption of both mineral and collagen that was inhibited by calcitonin [9007-12-9]. These hormones, however, had no influence on the release of procollagenase or collagenase either in the presence or in the absence of heparin. Once activated, bone collagenase digested the collagen of the bone explants, and more extensively after their

demineralization. Thus the latent collagenase that accumulates around non-resorbing bones has to be considered as a precursor and not as a residue of active enzyme. Active collagenase added to incipient cultures of bones disappeared with a half-life of 24 h. The lost enzyme could not, however, be reactivated by trypsin and thus was not transformed into latent procollagenase.

L9 ANSWER 37 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1979:52842 CAPLUS
DOCUMENT NUMBER: 90:52842
TITLE: Inhibition of mammary carcinoma invasiveness with cartilage-derived inhibitor
AUTHOR(S): Sadove, Alan Michael; Kuettner, Klaus E.
CORPORATE SOURCE: Dep. Gen., Rush-Presbyt.-St. Luke's Med. Cent., Chicago, IL, USA
SOURCE: Surgical Forum (1977), 28, 499-501
CODEN: SUFOAX; ISSN: 0071-8041
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Incubation of 30 human mammary carcinoma explants for 17 h with 17β-estradiol slightly increased the release of collagenase and protease activities when compared to untreated carcinoma explants. Incubation of the carcinoma with heparin resulted in a 3-fold stimulation of both enzyme activities when compared to 17β-estradiol-treated explants. Incubation of the carcinoma with cartilage resulted in a 100% decrease in collagenolytic activity when compared with untreated explants. The isolated cartilage collagenase inhibitor showed a dose-dependent inhibition of carcinoma explant collagenase activity. Histol. examination of the mammary carcinoma tissues disclosed degranulated mast cells, indicating that local heparin release may regulate tumor invasiveness.

L9 ANSWER 38 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1979:2207 CAPLUS
DOCUMENT NUMBER: 90:2207
TITLE: The purification of mouse bone collagenase by heparin-substituted Sepharose 4B affinity chromatography
AUTHOR(S): Sakamoto, S.; Sakamoto, M.; Goldhaber, P.; Glimcher, M. J.
CORPORATE SOURCE: Dep. Orthop. Surg., Harvard Med. Sch., Boston, MA, USA
SOURCE: Transactions of the Annual Meeting - Orthopaedic Research Society (1978), 3, 61
CODEN: TMOSDE; ISSN: 0149-6433
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Affinity chromatog. on heparin-Sepharose 4B was used in the purification of mouse bone collagenase following (NH4)2SO4 precipitation and DEAE-cellulose chromatog. The sp. activity of the enzyme was increased 26-fold by affinity chromatog. with an immediate recovery of activity of 80-100%. After gel-filtration on Sephadex G-200, the purified enzyme displayed a discrete single band on polyacrylamide gel electrophoresis in the presence or absence of Na dodecyl sulfate. The mol. weight of the purified collagenase was .apprx.47,000.

L9 ANSWER 39 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1978:485172 CAPLUS
DOCUMENT NUMBER: 89:85172

TITLE: Complete loss of heparin-releasable triacylglycerol lipase activity after collagense treatment of the rat liver
AUTHOR(S): Thomas, Josse; Debeer, Luc J.; Mannaerts, Guy P.
CORPORATE SOURCE: Lab. Pharmacol., Katholieke Univ. Leuven, Louvain, Belg.
SOURCE: Biochemical Journal (1978), 172(1), 177-9
CODEN: BIJOAK; ISSN: 0006-2936
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lipolytic activity at pH 8.5-9.5 was lowered by .apprx.80% in homogenates from rat livers perfused with **collagenase** (EC 3.4.24.3) [9001-12-1] (0.25 mg/mL) or heparin [**9005-49-6**] (50 units/mL). No heparin-releasable lipase (EC 3.1.1.3) [9001-62-1] activity was detected in hepatocytes isolated by **collagenase** treatment. Crude **collagenase** probably completely inactivated the plasma-membrane-bound heparin-releasable lipase.

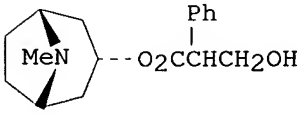
L9 ANSWER 40 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1977:66210 CAPLUS
DOCUMENT NUMBER: 86:66210
TITLE: Control of the interaction of cholesterol ester-rich lipoproteins with arterial receptors
AUTHOR(S): Day, Charles E.
CORPORATE SOURCE: Upjohn Co., Kalamazoo, MI, USA
SOURCE: Atherosclerosis (Shannon, Ireland) (1976), 25(2-3), 199-204
CODEN: ATHSBL; ISSN: 0021-9150
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Heparin [**9005-49-6**], **collagenase** [9001-12-1], lecithin, and succinylation caused 58-70% inhibition of 125I-labeled cholesterol ester-rich lipoprotein incorporation into rabbit aortic discs. Elastase [9004-06-2], papain [9001-73-4], trypsin [9002-07-7], neuraminidase [9001-67-6], β-glucuronidase [9001-45-0], and pancreatic lipase [9001-62-1] enhanced lipoprotein uptake by 2-4.5-fold. α-Amylase [9000-90-2], hyaluronidase [9001-54-1], and ribonuclease [9001-99-4] were without effect.

L9 ANSWER 41 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1977:25973 CAPLUS
DOCUMENT NUMBER: 86:25973
TITLE: Therapeutic effects of heparin on Pseudomonas-induced corneal ulceration
AUTHOR(S): Ellison, Arthur; Poirier, Robert
CORPORATE SOURCE: VA Hosp., San Antonio, TX, USA
SOURCE: American Journal of Ophthalmology (1976), 82(4), 619-27
CODEN: AJOPAA; ISSN: 0002-9394
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Exptl. corneal infections with P. aeruginosa in rabbits were treated with the antibiotics, polymyxin B [1404-26-8] (topical 3% solution every 2 hr) and colistin [1066-17-7] (topical 0.25% solution every 2 hr), given alone or as mixts. with the **collagenase** inhibitors, acetylcysteine (10% solution), edetate disodium (0.03 M), and heparin [**9005-49-6**] (solution of 2,500 units/ml). After 2 weeks treatment, the heparin-polymyxin

B mixture (I) [61067-53-6] decreased ulceration, corneal thinning, and descemetocele formation in comparison with polymyxin B treatment. Heparin (solution of 2500 units/ml, every 4 hr). was also used in combination with antibiotics to treat patients with Pseudomonas-induced corneal ulcers.

L9 ANSWER 42 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1977:11736 CAPLUS
DOCUMENT NUMBER: 86:11736
TITLE: Conditions governing the release of collagenase and procollagenase by bone explants in culture: effects of heparin
AUTHOR(S): Lenaers-Claeys, G.; Vaes, G.
CORPORATE SOURCE: Lab. Chim. Physiol., Univ. Louvain, Louvain, Belg.
SOURCE: Archives Internationales de Physiologie et de Biochimie (1976), 84(3), 634-6
CODEN: AIPBAY; ISSN: 0003-9799
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Heparin [9005-49-6] (50-300 μg/ml) added to a culture medium of mouse bone explants increased the release of procollagenase [39287-99-5] from the explants. Procollagenase appeared after a latency of 24-48 h and accumulated rapidly in 48-96 h. The treatment of the explants by repeated freezing and thawing blocked the release of procollagenase and of lysosomal enzymes. Heparin did not affect the release of collagenase [9001-12-1].

L9 ANSWER 43 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1976:586640 CAPLUS
DOCUMENT NUMBER: 85:186640
TITLE: Experimental study of the possibility of using compounds to depress the collagenase activity in the cornea
AUTHOR(S): Toczolowski, Jerzy
CORPORATE SOURCE: Klin. Okulistycznej, Akad. Med., Lublin, Pol.
SOURCE: Klinika Oczna (1976), 46(8), 865-70
CODEN: KOAOAE; ISSN: 0023-2157
DOCUMENT TYPE: Journal
LANGUAGE: Polish
GI



I

AB Corneal ulceration was induced in rabbits by cauterization. Subsequent treatment with Mucomyst [616-91-1], heparin [**9005-49-6**], and atropine (I) [51-55-8] completely cured the ulceration within 5 days in all 5 animals tested by inhibiting **collagenase** [9001-12-1] activity. Treatment for the same length of time with only Mucomyst and I had a curative effect in 4 of 5 animals. Treatment with only I was effective in only 3 of 5 animals.

L9 ANSWER 44 OF 45 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1975:120789 CAPLUS
DOCUMENT NUMBER: 82:120789
TITLE: Interaction between heparin and mouse bone collagenase
AUTHOR(S): Sakamoto, Seizaburo; Sakamoto, Masako; Goldhaber, Paul; Glimcher, Melvin J.
CORPORATE SOURCE: Med. Cent., Child. Hosp., Boston, MA, USA
SOURCE: Biochimica et Biophysica Acta (1975), 385(1), 41-50
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mouse bone collagenase was tightly bound to a heparin-substituted gel at low ionic strength. The bond was reversible, however, and the collagenase could be eluted at high ionic strength. In addition to providing a method for purifying the enzyme with high yield, the results suggest that the strong ionic bond between heparin and collagenase may partially explain the mechanism wherein heparin enhances the activity of mouse bone collagenase.

L9 ANSWER 45 OF 45 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1973:450228 CAPLUS
DOCUMENT NUMBER: 79:50228
TITLE: Mouse bone collagenase. Effect of heparin on the amount of enzyme released in tissue culture and on the activity of the enzyme
AUTHOR(S): Sakamoto, Seizaburo; Goldhaber, Paul; Glimcher, Melvin J.
CORPORATE SOURCE: Harvard Sch. Dent. Med., Boston, MA, USA
SOURCE: Calcified Tissue Research (1973), 12(3), 247-58
CODEN: CATRBZ; ISSN: 0008-0594
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The amount of mouse bone collagenase recovered in the tissue culture medium of bone cultured in vitro was increased by the addition of heparin at an optimal concentration of .apprx. 50 units/ml of tissue culture medium. Dextran sulfate and Treburon (a synthetic polysaccharide-sulfuric ester) which are structurally and chemically related to heparin were as effective as heparin in increasing the amount of mouse bone collagenase recovered in the tissue culture medium. In addition to stimulating the synthesis and (or) release of mouse bone collagenase, heparin also increased the specific activity of both crude and purified preparation of the enzyme when assayed using collagen in the solid state as the substrate, but showed no enhancement of enzyme activity when assayed using collagen in solution as the substrate. Dextran sulfate was as effective as heparin in increasing the activity of the enzyme using collagen in the solid state as a substrate. Neither heparin or dextran sulfate enhanced the activity of Clostridium histolyticum collagenase. For the first time, a purified tissue collagenase has been shown to both degrade and solubilize undenatured, insoluble tissue collagen at 37°. Moreover, since this action was markedly enhanced by the addition of heparin, it suggests that heparin and similar substances may play an important role in the regulation of collagen degradation during the remodeling of collagenous tissues in vivo.